Claims

1. An *in vitro* method of generating insulin producing beta cells from a population comprising dedifferentiated exocrine pancreatic cells of a first mammal, said method comprising the steps of:
   -a) providing a population comprising dedifferentiated exocrine pancreatic cells in a culture medium
   -b) adding one or more ligands of the gp130 receptor of a second mammal and/or adding one or more ligands of the EGF receptor of a third mammal to said culture medium,
   -c) incubating said dedifferentiated exocrine pancreatic cells in said culture medium comprising said one or more ligands of the gp130 receptor and/or said one or more ligands of the EGF receptor.

2. The method according to claim 1 wherein said ligand of said gp130 receptor is a human or humanised ligand of said gp130 receptor.

3. The method according to claim 3 or 2, wherein said ligand of said gp130 receptor is LIF.

4. The method according to any of claims 1 to 3, wherein the ligand of said gp130 receptor is human or humanised LIF.

5. The method according to claim 3 or 4, wherein LIF is added to said culture medium in a concentration between 10 and 100 ng/ml.

6. The method according to claim 1, wherein said ligand of said EGF receptor is a human or humanised ligand of said EGF receptor.

7. The method according to claim 1 or 6, wherein said ligand of said EGF receptor is EGF.

8. The method according to claim 6 or 7, wherein said ligand of said EGF receptor is human or humanised EGF.

9. The method according to any of claims 6 to 8, wherein EGF is added to said culture medium in a concentration between 10 and 100 ng/ml.

10. The method according to any of claims 1 to 9, wherein the method further comprises the step of adding bFGF to said culture medium during step b).

11. The method according to any of claims 1 to 10, wherein in step b) one or more of said ligands of the gp130 receptor and/or one or more of said ligands of said EGF receptor are added to said culture medium in a concentration between 1 and 10 000 ng/ml.

12. The method according to any of claims 1 to 11, wherein said medium is free from KGF or a gastrin/CCK receptor ligand.

13. The method according to any of claims 1 to 12, wherein said incubation step is performed during less than 5 days.

14. The method according to any of claims 1 to 13, wherein the population comprising dedifferentiated exocrine pancreatic cells is selected from the group consisting of duct cells, acinar cells and islet cells.

15. The method according to any of claims 1 to 14, further comprising, prior to step a), a preliminary step of depleting said population from beta cells.

16. The method according to any of claims 1 to 15, wherein the mammalian cells are human cells.

17. The method according to any of claims 1 to 16, wherein the mammalian cells are rat cells, wherein one or more ligands of said EGF receptor

comprise human EGF and/or wherein said one or more ligands of gp130 receptor comprise murine LIF.

18. A population of mammalian pancreatic cells comprising mammalian insulin producing beta cells obtainable by a method according to any of claims 1 to 17.

19. The population of mammalian pancreatic cells according to claim 18, wherein said population comprises from about 5 to about 15 percent of insulin-positive cells.

20. A population of mammalian pancreatic cells according to claim 18 or 19, wherein said cell population after exposure to 20 mM glucose for 4 hours at 37 °C in RPMI-1640 medium supplemented with 10% fetal bovine serum shows a more than 2 fold increase in insulin secretion when compared to the insulin secretion prior to said exposure to glucose.

21. A population of mammalian pancreatic cells according to claim 18 or 19, being able to provide an insulin secretion of at least 10 ng/ml after exposure of said population to 20 mM glucose for 4 hours at 37°C in RPMI-1640 medium supplemented with 10% fetal bovine.

22. A population of mammalian cells comprising mammalian insulin producing beta cells, wherein said cell population comprises cells having at least one feature of a differentiated beta cell and at least one feature of an undifferentiated beta cell in the same individual cell.

23. The population of mammalian pancreatic cells according to claim 22, wherein a feature of a differentiated beta cell is insulin secretion and wherein a feature of an undifferentiated beta cell is CK20 expression and/or binuclearity.

24. A population of mammalian pancreatic cells according to claim 22 or 23, obtainable by the method of any of claims 1 to 18.

25. A population of mammalian pancreatic cells comprising mammalian insulin secreting beta cells wherein said cell population comprises a first subpopulation of cells having markers of undifferentiated or dedifferentiated cells and comprises a second subpopulation of cells having markers of differentiated cells.

26. The population of mammalian pancreatic cells according to claim 25, wherein the markers of differentiated cells are selected from the group of consisting of C-peptide-I, Pdx-1, Glut-2 and insulin.

27. The population of mammalian pancreatic cells according to claim 26, wherein the markers of dedifferentiated or undifferentiated cells are selected from the group of cytokeratin 7, cytokeratin 19, cytokeratin 20, CCKB receptor for gastrin, PGP9.5 and notch-1 receptor.

28. A population of mammalian pancreatic cells according to any of claims 18 to 27, being obtainable by the method of any of claims 1 to 17.

29. The population of mammalian pancreatic cells according to any of claims 18 to 28, wherein said mammalian cells are human cells.

30. The population of mammalian pancreatic cells according to any of claims 18 to 29, wherein said mammalian cells are porcine cells.

31. The population of mammalian pancreatic cells according to any of claims 18 to 30, wherein said mammalian cells are rat cells.

32. A pharmaceutical composition comprising a therapeutically active amount of a mammalian pancreatic cell population according to any of claims 18 to 31, and at least one pharmaceutically acceptable carrier.

33. Use of a mammalian pancreatic cell population according to any of claims 18 to 31, for the manufacture of a medicament.

34. Use according to claim 33, wherein the medicament is used for the treatment of diabetes type 1 or type 2.

35. A method for the treatment of diabetes type 1 or type 2 comprising the step of administering an effective amount of the pharmaceutical composition of claim 32 to an individual in need of it.

36. Use of a combination of a human or humanised ligand of a EGF receptor, and a human or humanised ligand of the gp130 receptor for the preparation of a medicament.

37. Use according to claim 36, wherein said medicament is used for the treatment of diabetes type 1 or type 2.

38. Use according to claim 36 or 37, wherein the human or humanised ligand of a EGF receptor is human EGF and the human or humanised ligand of the human gp130 receptor is human LIF.

39. Use of a human or humanised ligand of the gp130 receptor for the preparation of a medicament for the treatment of diabetes type 1 or type 2.

40. Use according to claim 39, wherein said human or humanised ligand of the gp130 receptor is LIF.

41. An *in vitro* method for determining the degree of redifferentiation of dedifferentiated mammalian pancreatic cells comprising the steps of determining one or more parameters selected from the group consisting of:
a) The presence of CK20, CK7 or CK 19
b) the ocurrence of binucleated cells
c) the presence of insulin positive cells
d) the presence of C-peptide, Pdx-1 and Glut-2
e) the presence of gastrin CCKB receptor, PGP9.5 and notch-1 receptor on said mammalian pancreatic cells.

42. A population of mammalian pancreatic cells according to any of claim 18 to 31, being identifiably by the method of claim 41.

43. A method of generating *in vitro* insulin producing mammalian beta cells from dedifferentiated pancreatic cells comprising the step of:
-incubating said dedifferentiated pancreatic cells in a medium comprising a ligand of the gp130 receptor.

44. The method according to claim 44 wherein the medium further comprises a ligand of the EGF receptor.